REMARKS

Rejection of the claims under 35 U.S.C.§103

The Examiner maintains the rejection of the claims under 35 U.S.C.§103 as being obvious over Dianov et al. combined with McCarthy et al. US '176. Applicant traverse this rejection and withdrawal thereof if respectfully requested.

Applicants contend that a skilled artisan is not motivated to combine the references for the following reasons.

A. There is no motivation to combine the references because the proposed modification would make Dianov *et al.* unsatisfactory for its intended purpose.

The Dianov *et al.* reference teaches synthetic oligonucleotides, which each contain a single base that serves as a glycosylase substrate. This modified base is introduced into the oligonucleotides during artificial synthesis. The Examiner asserts that the oligonucleotides of Dianov *et al.* may be modified according to the teaching of the '176 reference. That is, the single aberrant base of Dianov *et al.* may be introduced into the oligonucleotides *via* enzymatic extension, and then subsequently, a 3'-OH end of an extendable DNA fragment may be formed.

However, applying the modification of the '176 reference to the oligonucleotides of Dianov *et al.* will result in more than a single base modification. According to the '176 reference at column 5, lines 49-53 "amplification will typically involve amplifying a target nucleic acid sample using a combination of normal DNA precursor nucleotides and one or more modified precursor nucleotide(s) where the modified precursor nucleotide replaces one of the normal precursor nucleotides." For example, as shown in Figure 1 of the '176 reference, dUTP replaces dTTP during amplification, and all of the thymine bases are replaced with uracil. Likewise, all of the thymine or guanine or cytosine or adenine bases in the Dianov *et al.* oligonucleotides would be replaced with the modified base of choice according to the '176 reference. As is evident from the Dianov *et al.* oligonucleotides depicted in Figure 2, (page 1607 of Dianov *et al.*), the enzymatic extension described in the '176 reference would result in multiple modified bases in the Dianov *et al.* oligonucleotides.

The incorporation of multiple modified bases into the oligonucleotides of Dianov *et al.* would render them unsatisfactory for their purpose. The purpose of the oligonucleotides in the

Dianov *et al.* reference is to use them to demonstrate the mechanism of DNA repair of a *single* aberrant base. Because mechanisms of DNA repair vary and depend, *inter alia*, upon the number and location of aberrant bases that require repair, modifying the oligonucleotides of Dianov *et al.* according to the enzymatic extension procedure of the '176 reference, would not have allowed Dianov *et al.* to describe the pathway of single base repair.

More specifically, the purpose of the Dianov *et al.* reference is to answer the "critical question" (page 1611, first column second paragraph, Dianov *et al.*) of whether or not repair of a single aberrant base is 1 or 2 nucleotides in size. Dianov *et al.* answered this critical question by using synthetic double stranded oligonucleotides with sequences suited for restriction enzyme analysis. For example, in order to determine whether or not repair occurs 3' to a single modified base, Dianov *et al.* constructed a particular oligonucleotide sequence, termed "substrate c." This oligonucletoide is AT rich in the region of the single modified base. The oligonucleotide was designed in this manner so that if repair of the modified base occurred 3' to the AP site, a marker in a 13 nucleotide fragment would be apparent after *SacI* digestion.

Hence, modifying the Dianov *et al.* oligonucleotides according to the '176 reference would not only have resulted in numerous aberrant bases, thus rendering the purpose of Dianov *et al.* impossible, but in the case of one of the oligonucleotides, substrate c, the AT rich regions would have been lost, resulting in the loss of the *SacI* restriction site. These changes would have resulted in non-interpretable data.

Thus, the oligonucleotides of Dianov *et al.* cannot be modified by the enzymatic extension of the '176 reference without rendering the prior art invention unsatisfactory for its intended purpose. "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Therefore, combining the Dianov *et al.* reference with the '176 reference is improper.

B. There is no motivation to combine the references because the prior art does not suggest the desirability of the claimed invention.

Moreover, even if the Examiner were to find that the '176 modification of the Dianov *et al.* reference is not unsatisfactory for its intended purpose, the prior art must suggest the desirability of the claimed invention. "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed...combination..." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Applicants contend that the desirability of the instant invention is not suggested by the combination of the Dianov *et al.* reference and the proposed modification of the '176 reference.

The instant invention concerns the characterization of a nucleic acid molecule template of interest *via* the extension of a 3'-OH end of an extendable DNA fragment on the nucleic acid molecule template of interest. The present invention is used, *inter alia*, to identify one or more bases in a nucleic acid of interest that were previously unknown. Additionally, the extendable fragment may be used to determine whether or not a particular sequence contains a single nucleotide polymorphism or other mutation, which is unknown for a particular sample. The combination of the Dianov *et al.* reference with the modification of the '176 reference does not suggest these desirable features.

The Dianov *et al.* reference is concerned with DNA repair of a *single* aberrant base. "[t]he main finding in the present work...is that the prevalent repair reaction involves the filling-in of a gap of only a single nucleotide" (page 1610, column 2, paragraph 2). Additionally, the constitution and location of the single repaired base of Dianov *et al.*, unlike the characterization of one or more bases in the nucleic acid template of interest of the present invention, is a base, which is known to the skilled artisan *before* extension of the alleged extendable fragment. That is, during the generation of the alleged extendable fragment of Dianov *et al.*, as combined with the '175 reference, a known base is replaced with a modified base. Thus, the constitution of the replaced/repaired base is known because, according to the '176 reference, modified bases replace known bases (*e.g.* uracil replaces thymine).

Additionally, the location of the replaced/repaired base, also, is known before extension of the alleged extendable fragment of Dianov *et al.* The modified base of Dianov *et al.*, which corresponds to the replaced base, is removed *via* glycosylase. Cleavage then occurs to form the alleged 3'-OH end of an extendable DNA fragment. Thus, the skilled artisan recognizes that the location of the replaced/repaired base is found on the strand complementary to the alleged 3'-OH end of an extendable DNA fragment, *i.e.* one base 3' to the end of the alleged 3'-OH end of the extendable DNA fragment on the opposite strand.

Subsequently, the alleged 3'-OH end of the extendable DNA fragment is extended, but *only to repair the previously identified base; no additional unknown bases are identified.* ("These data demonstrate that the majority of DNA repair replication events in the *E. coli* cell extract involved the replacement of only one nucleotide." (page 1609, first column, lines 6-8. Dianov *et al.*)).

Furthermore, the Dianov *et al.* reference suggests that no further bases *could* be identified with the alleged 3'-OH end of the extendable DNA fragment using the template as shown in Figure 9. The pathway for single base repair, which is depicted on the left side of Figure 9 (the right side depicts the pathway that *rarely* occurs) shows that the alleged 3'-OH end of the extendable DNA fragment could *not* be further extended because it is blocked by a second 5' to 3' fragment.

Therefore, the skilled artisan is not provided with combined references that suggest that unknown bases can be identified with the alleged 3'-OH end of the extendable DNA fragment of Dianov *et al.* Applicants contend that an inventive step would be required to determine how the alleged 3'-OH end of the extendable DNA fragment of Dianov *et al.*, as modified by the '176 reference, could be used to identify unknown bases on selected templates.

Thus, because the desirable features of the present invention, that of identifying unknown bases, is not suggested by the Dianov *et al.* reference using the proposed modification of the '176 reference, the combination of the references is improper and the 103(a) rejection should be withdrawn.

In view of the above remarks, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD Reg. No. 40,069at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By _____

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